

# The ethics of preconception expanded carrier screening in patients seeking assisted reproduction

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**ABSTRACT:** Expanded carrier screening (ECS) entails a screening offer for carrier status for multiple recessive disorders simultaneously and allows testing of couples or individuals regardless of ancestry or geographic origin. Although universal ECS—referring to a screening offer for the general population—has generated considerable ethical debate, little attention has been given to the ethics of preconception ECS for patients applying for assisted reproduction using their own gametes. There are several reasons why it is time for a systematic reflection on this practice. Firstly, various European fertility clinics already offer preconception ECS on a routine basis, and others are considering such a screening offer. Professionals involved in assisted reproduction have indicated a need for ethical guidance for ECS. Secondly, it is expected that patients seeking assisted reproduction will be particularly interested in preconception ECS, as they are already undertaking the physical, emotional and economic burdens of such reproduction. Thirdly, an offer of preconception ECS to patients seeking assisted reproduction raises particular ethical questions that do not arise in the context of universal ECS: the professional's involvement in the conception implies that both parental and professional responsibilities should be taken into account. This paper reflects on and provides ethical guidance for a responsible implementation of preconception ECS to patients seeking assisted reproduction using their own gametes by assessing the proportionality of such a screening offer: do the possible benefits clearly outweigh the possible harms and disadvantages? If so, for what kinds of disorders and under what conditions?

**Key words:** expanded carrier screening / assisted reproduction / genetic testing / non-invasive prenatal diagnosis / ethics / proportionality / screening offer

## Introduction

Expanded carrier screening (ECS) refers to screening for multiple (mostly) autosomal and X-linked recessive disorders at the same time and allows testing of individuals or couples regardless of ancestry or geographic origin. 'Universal' ECS—defined as a carrier screening offer to all prospective parents, regardless of their a priori carrier risk—has generated considerable ethical debate (Langlois *et al.*, 2015; van der Hout *et al.*, 2017; Chokoshvili *et al.*, 2018; Kraft *et al.*, 2019).

However, little attention has been given to the ethics of 'selective' ECS for patients applying for assisted reproduction using only their own gametes (the ethics of ECS in donor conception was previously addressed by ESHRE (Dondorp *et al.*, 2014)). There are several reasons why also a systematic reflection on the ethics of ECS as offered to patients seeking assisted reproduction using their own gametes is urgently needed. Firstly, various European fertility clinics already offer ECS on a routine basis (Martin *et al.*, 2015; Abuli *et al.*, 2016; Gil-Arribas *et al.*, 2016), and others are considering a similar practice.

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Professionals involved in assisted reproduction have indicated a need for ethical guidance with regard to the option of offering ECS to couples applying for assisted reproduction because of either subfertility or a high genetic risk of having an affected child (personal communications). Secondly, it is expected that patients seeking assisted reproduction will be particularly interested in ECS, as they are already undertaking the (physical, emotional and economic) burdens of IVF or other forms of assisted reproductive technologies (ART) (Cho et al., 2013; Franasiak et al., 2016). This may hold true especially for those turning to assisted reproduction in order to avoid the transmission of a known disease-causing variant to their children. As their embryos will already be subjected to preimplantation genetic testing for monogenetic diseases (PGT-M)—formerly known as preimplantation genetic diagnosis (PGD)—the option to simultaneously avoid the transmission of other serious disorders (by adding ECS to the patients' work-up) may well be an appealing option. Thirdly, an offer of ECS to patients applying for assisted reproduction raises particular ethical questions that do not arise in the context of universal ECS: the involvement of professionals in the conception implies that from a moral point of view, both parental and professional responsibilities should be taken into account.

This paper reflects on and provides ethical guidance for a responsible implementation of ECS to patients seeking assisted reproduction. The questions to be addressed are:

*Is the offer of ECS to all patients seeking assisted reproduction using their own gametes proportionate, i.e.: do the possible benefits of such screening clearly outweigh the possible harms and disadvantages? If so, for what kinds of disorders and under what conditions?*

In answering these questions, we will take account of the fact that in some countries carrier screening is already available—either on a public or private basis—while other countries do not (yet) offer any form of carrier screening.

This paper first sketches relevant (technological) developments in the field of carrier screening and outlines some current ECS-in-assisted-reproduction practices in Europe and the USA. Second, ethical issues relevant to the implementation of ECS in assisted reproduction will be addressed, culminating, finally, in a set of recommendations. Although this paper concentrates on the ethics of an ECS offer to patients applying for assisted reproduction, it should be noted that some considerations may also have implications for the general debate about ECS.

Before we move on, we would like to make one note of clarification. Carrier screening can be performed in the preconception or prenatal period. In the context of assisted reproduction, an offer of ECS will be in the preconception stage. To avoid any misunderstandings, in the remainder of this document the term 'preconception ECS' will be used.

All abbreviations used in the paper are listed in Table I.

## Background and facts

Over the past two decades, more than 1300 recessively inherited (autosomal or X-linked) disorders have been identified, with a mild to severe impact on health and prospected lifespan (Henneman et al., 2016). Carriers of autosomal recessive disorders have only one copy

**Table I Abbreviations used in discussion of the ethics of preconception expanded carrier screening in ART.**

ACCE	Analytic validity, clinical validity, clinical utility, and ethical, legal, and social issues
AD	Autosomal dominant
ART	Assisted reproductive technologies
CF	Cystic fibrosis
ECS	Expanded carrier screening
FM	Full mutation
FXS	Fragile X syndrome
FXTAS	Fragile X-associated Tremor/Ataxia Syndrome
IVF	<i>In vitro</i> fertilization
MAR	Medically assisted reproduction
Mt	Mitochondrial
NBS	New-born screening
NGS	Next-generation sequencing
NIPD	Non-invasive prenatal diagnosis
PCS	Preconception carrier screening
PGT	Preimplantation genetic testing
PGT-A	Preimplantation genetic testing for aneuploidy (formerly termed preimplantation genetic screening or PGS)
PGT-M	Preimplantation genetic testing for monogenetic diseases
PM	Pre-mutation
POI	Premature ovarian insufficiency
SCD	Sickle cell disease
VOUS	Variants of unknown clinical significance
WESA/WGSA	Whole exome/genome sequencing and analysis

of the mutated gene and usually do not show any symptoms of the disease. However, couples that carry disease-causing variants in the same gene on autosomes have a 1-in-4 risk with each pregnancy that their child will inherit both mutated genes and develop the disease. When a woman is a carrier of an X-linked disorder, her male offspring has a 1-in-2 risk of being affected. In this paper, the term 'carrier couple' refers to couples of whom both partners have a so-called class 4 or 5 variant in the same autosomal recessive disease gene as well as to couples of whom the female partner is carrier of an X-linked disorder. Whereas class 4 variants have a high likelihood of being pathogenic, class 5 variants are considered to be definitely pathogenic.

In some countries, diagnostic testing for carrier status of recessive disorders has been offered to relatives of a proband for many years, as part of regular clinical genetics. In addition, some ethnic communities with a higher prevalence of particular recessive disorders have introduced carrier screening for its members, irrespective of their family history. Well-known examples of the so-called 'ancestry-based carrier screening' are beta-thalassaemia carrier screening in several high-risk populations in the Mediterranean region (Cousens et al., 2010) and premarital carrier screening for recessive diseases more prevalent among members of the Ashkenazi Jewish population, such as Tay–Sachs disease, Canavan disease and Bloom syndrome (Kaback, 2000; Wailoo and Pemberton, 2006). A more recent development is the promotion of universal approaches that offer carrier screening to

all individuals regardless of ethnicity or family history, for instance carrier screening for cystic fibrosis (CF) in the USA ([American College of Obstetricians and Gynecologists, 2011](#)).

While in the past, carrier screening mainly involved a single or only a few disease-causing variants, the availability of new genomic testing possibilities has given carrier screening new impetus: next-generation sequencing (NGS) technologies allow for efficient and affordable screening of hundreds of disease-causing variants at the same time ([Grody et al., 2013](#)). Such ECS is expected to provide valuable information for people who do not belong to a traditional 'high-risk' population. Although rare individually, it is estimated that at least 1 in 100 couples of the general population are at high risk of having a child with a serious recessive disorder ([Edwards et al., 2015](#); [Grody, 2016](#); [American College of Obstetricians and Gynecologists, 2017](#)). Some commentators, arguing that the risk of having a child affected with a serious recessive condition could be between 0.25 and 0.5%, stipulate that this risk is in the same order of magnitude as the risk for a 37-year-old woman of having a child with Down syndrome ([Ropers, 2012](#)).

In developed countries, recessive disorders collectively account for ~20% of infant mortality and 10% of paediatric hospitalizations ([Costa et al., 1985](#), [Kumar and Jumali, 2006](#)). The ultimate chance of giving birth to a live born child with a recessive disorder is a combination of carrier risk, the risk of *de novo* variants in the embryos, and the potential of the affected foetus to survive to term. Carrier screening only measures carrier risk and cannot reveal the occurrence of *de novo* variants.

Carrier screening can be performed either before or during pregnancy. Preconception carrier screening (PCS) has the advantage of allowing a wider range of reproductive options than only prenatal diagnosis followed by a possible termination of pregnancy. These choices include gamete donation and PGT-M, opting for adoption and refraining from parenthood. However, as many pregnancies are not planned, PCS has not been widely used in the past except by some ethnic groups, especially Ashkenazi Jews, and in countries that have made such screening mandatory before couples are given approval to get married. For instance, couples in Iran, Saudi Arabia and Cyprus are legally obliged to participate in premarital carrier screening for haemoglobinopathies ([Cousens et al., 2010](#)). Since pregnant women generally receive medical attention, some health specialists and reproductive counsellors consider prenatal carrier screening rather than PCS the most practical—but not necessarily the most ethical—approach ([Henneman et al., 2016](#)).

In the context of assisted reproduction, it is much easier to reach potentially interested couples in the preconception period. In European countries, 2–6% of births are achieved by means of ART ([Calhaz-Jorge et al., 2017](#)). Couples who have already undertaken the physical, emotional and economic burdens of fertility treatment may well be particularly positive towards carrier screening, as this can be easily added to a planned IVF cycle and may increase the chances of having a healthy child. As mentioned above, this applies even more to couples who are eligible for PGT-M, whose primary concern is the possible transmission of genetic disease to their children. Genetics professionals from the USA who were asked to assess the potential benefits and challenges of preconception ECS in reproductive healthcare, indicated that 'the additional demands associated with ECS and PGD (following the identification of a shared genetic risk) would be lower

for IVF patients than for other couples' ([Cho et al., 2013](#)) (but see also the section 'Proportionality'). [Franasiak et al.](#) likewise state that 'preconception genetic testing and counselling are important for patients undergoing infertility care. This unique population allows for thorough counselling and the opportunity to test for a variety of inheritable diseases prior to conception when in vitro fertilization and pre-implantation genetic diagnosis are used' ([Franasiak et al., 2016](#)).

In the last few years, a number of fertility clinics in Europe started offering preconception ECS to couples undergoing IVF or other forms of ART ([Martin et al., 2015](#); [Abuli et al., 2016](#); [Gil-Arribas et al., 2016](#)). In 2015, [Martin et al.](#) published a study in which 138 couples seeking assisted reproduction using their own gametes were undergoing preconception ECS for more than 600 disease phenotypes. Seven couples were identified as carrier couples. These couples received genetic counselling and were advised to opt for PGT-M. At time of writing, four of the identified carrier couples had decided to start a PGT-M trajectory ([Martin et al., 2015](#)). Larger follow-up studies are needed to describe the actual uptake of PGT-M, or alternatively gamete donation, after ECS.

## Ethical reflections

When considering or providing preconception ECS to patients seeking assisted reproduction, clinicians should always take into account the relevant medico-legal norms in their countries' jurisdictions. This section concentrates on the ethics of such screening. While some of the issues to be addressed specifically relate to preconception ECS to patients seeking assisted reproduction, other issues are also relevant for normative reflections on (preconception) ECS generally.

### The aim of preconception ECS in assisted reproduction: autonomy or prevention?

Until the 1980s, many health professionals considered prevention—in the sense of reducing the birth prevalence of serious disorders—the primary aim of reproductive screening, both during and before pregnancy. For instance, in an influential paper, public health epidemiologists Zena Stein and Mervyn Susser advocated prenatal diagnostic testing and elective termination of pregnancy as preventative measures to reduce the incidence of Down syndrome at birth ([Stein and Susser, 1971](#); [Porter, 1982](#)). Not surprisingly, this emphasis on prevention was soon felt to raise serious ethical concerns, especially with regard to screening for abnormalities during pregnancy. These concerns were 2-fold. Firstly, however, much it is stressed that screening should enable women to make their own decisions, it is difficult to see how an account of prenatal screening as aimed at reducing the number of children born with the relevant conditions would not promote nudging women into making the 'right', i.e. 'preventative', reproductive choices. Considering the moral sensitivity and emotional impact of abortion, it would be problematic to pressure women into terminating a desired pregnancy. Secondly, the prevention view has invited the criticism of disability rights' advocates, according to whom the practice reflects a discriminatory attitude towards people living with the relevant conditions ([Parens and Asch, 2000](#)). In order to avoid these moral challenges, official (Western) accounts of the aim of prenatal screening have moved away from the language of prevention and accepted the

so-called autonomy paradigm, meaning that such screening should enable individual pregnant women (and their partners) to make meaningful reproductive choices with regard to having or not having a child with a serious disorder or disability (de Jong and de Wert, 2015; Dondorp et al., 2015).

In the context of carrier screening, we can observe a more diffuse picture regarding the primary aim of screening. In accordance with the first prenatal screening programmes, most ancestry-based carrier screening initiatives dating from the 1950s intended to avoid the birth of children with serious genetic conditions. With regard to more recently introduced ancestry-based carrier screening programs, the picture becomes less clear; in describing their goals, many of these programmes include elements of both the autonomy and the prevention paradigms. For instance, the Jewish Genetic Disease Consortium describes the goal of carrier screening as ‘decreas[ing] the incidence of Jewish genetic diseases and assure healthy families by increasing preconception carrier screening rates and promoting the understanding of reproductive options available to carrier couples’. In many Western countries, an unambiguous embrace of the autonomy paradigm accompanied the introduction of universal carrier screening—i.e. a targeted or ECS offer to *all* individuals or couples of reproductive age (Laberge et al., 2010; Edwards et al., 2015; Nazareth et al., 2015). The goal to enable autonomous reproductive choice is, for instance, reflected in a policy paper about ECS by the European Society of Human Genetics (Henneman et al., 2016).

How to explain the difference between the paradigms underlying ancestry-based and universal carrier screening? There are various reasons why many stakeholders—including prospective parents—consider ‘prevention’ a justified aim of ancestry-based carrier screening. Firstly, couples belonging to an ethnic community with a higher prevalence of particular recessive disorders often have close experience with the distress of parents whose child is born with a genetic disease or disability; they want to ensure that they do not suffer the same fate. Secondly, it should be noted that many programmes aimed at prevention offer carrier screening *before*, and not during pregnancy. Apparently, a programme’s pursuit of prevention is considered less problematic in the preconception period. The reason for this is that before pregnancy, carrier couples have the largest range of reproductive options at their disposal, including gamete donation and PGT-M. Passing on a genetic disorder to one’s offspring increasingly becomes a controllable factor in a sense that would not entail emotional and morally highly sensitive decision-making concerning pregnancy termination.

## Parental responsibilities

Do prospective parents have a moral obligation to take preventative measures if they have the means to avoid the conception of a severely affected child without disproportionate cost to themselves? This question does not only emerge in the context of ancestry-based PCS, but may be relevant for *all* PCS initiatives, including preconception ECS to patients seeking assisted reproduction.

In families without an *a priori* increased carrier risk, the birth of an affected child typically comes as a surprise. Preconception ECS would enable these families to be informed timely about their carrier risk and reduce the chance of conceiving a child with a severe genetic disorder. However, is it reasonable to expect that couples who do not belong to a high-risk group participate in preconception ECS? Would it not

be more appropriate to merely inform them about possible participation in such screening and thus to increase their reproductive autonomy? Presenting preconception ECS as a ‘reproductive code of conduct’ for all couples who wish to have children may be too high a price (van der Hout et al., 2019). However, one could also argue that the relevant responsibility of prospective parents does not (just) depend on the magnitude of their risk of being a carrier couple, but (also) on the severity of the disease under consideration (Clarkeburn, 2000). An in-between position, accepted in the present document, would be that prospective parents, given their generally low *a priori* risk, do not have a moral responsibility to take part in preconception ECS, but that proven carrier couples, given their high risk, may have a conditional moral responsibility to opt for avoidance, at least if the disorder in question is serious. Please note that this view does not justify any legal constraints on reproductive decision-making.

## Professional responsibilities

An offer of preconception ECS to patients applying for assisted reproduction raises particular ethical questions (that do not arise in other PCS contexts) of professional responsibility. It is widely accepted that professionals involved in assisted reproduction do not only have the responsibility to assist couples in achieving a pregnancy; they are also expected to take into account the welfare of the child that they are causally and intentionally involved in creating. As stated by, amongst others, the ESHRE Task Force on Ethics and Law, the physician must take into account presently known risk factors for the welfare of the future child (Pennings et al., 2007). Risk factors that may have implications for the welfare of the child include both medical conditions of potential parents and psychosocial factors. To decide whether actual risk factors are a valid reason for refusing assistance in reproduction, ESHRE has recommended the ‘reasonable welfare’ standard. This standard entails a moral duty to refrain from providing assistance in cases where there is high risk that the child will have a seriously diminished quality of life. Moreover, above this bottom-line, professionals involved are expected to limit health risks to the future child where doing so is reasonably possible.

What follows from these professional norms with regard to offering preconception ECS to patients seeking assisted reproduction? May (or should) professionals recommend, or even insist, that patients one, undergo preconception ECS, and two, make use of ‘preventative measures’ (PGT-M, gamete donation or prenatal diagnosis) when the couple has been identified as a carrier couple? And how would such professional ‘directivity’ relate to the above-discussed tension between a couple’s reproductive autonomy and their parental responsibility? Various scenarios (including a ‘mixed’ scenario) for the implementation of a preconception ECS trajectory for patients seeking assisted reproduction can be distinguished based on either a *non-directive* offer with the autonomy paradigm as the leading principle, or a *directive* offer that considers the patient’s acceptance of this trajectory to be a precondition for having access to assisted reproduction, taking into account professional and parental responsibilities for the welfare of the future child (Fig. 1) (De Wert, 2016).

The implications of a non-directive offer are 2-fold. First, regarding Step 1, it implies that patients should decide for themselves whether they want to participate in the preconception ECS offered. A similar line of reasoning applies to Step 2: the counselling trajectory should

	Step 1: Preconception ECS	Step 2: Reproductive options, including PGT-M, and donor gametes
(a) <b>Non-directive approach</b>	Offer ECS in order to facilitate patients' well-informed decision making	Inform carrier couples about all reproductive options available, aimed at facilitating their well-informed decision making
(b) <b>Directive approach</b>	Offer ECS as a precondition for access to assisted reproduction, in order to account for professional and parental responsibility	Offer preventive options, like PGT-M and donor gametes, as a precondition for carrier couples' access to assisted reproduction, in order to account for professional and parental responsibility

**Figure 1. Scenarios for a preconception expanded carrier screening trajectory for patients seeking assisted reproduction.** ECS, expanded carrier screening; PGT-M, preimplantation genetic testing for monogenetic diseases.

enable proven carrier couples to make a well-informed decision with regard to reproduction. Whatever the couples decide, they will be assisted in conceiving a child. The alternative directive policy implies, firstly, that patients are expected to participate in this screening as a precondition for assisted reproduction (Step 1). If patients turn out to be a carrier couple, Step 2 implies that they will only have access to assisted reproduction if they are prepared to substantially reduce the risk of conceiving an affected child by means of 'preventative measures', to be further specified (see below).

Which policy is morally preferable? We recommend that for both Steps 1 and 2 in the trajectory, this depends on first, the level of genetic risk; and second, the severity of the disease under consideration (in line with a former ESHRE-document on handling the risks of consanguinity in the context of intra-familial medically assisted reproduction) (ESHRE Task Force on Ethics and Law *et al.*, 2011).

Step 1: If patients seeking assisted reproduction have an *a priori* low carrier risk, we suggest that preconception ECS should be offered only in a non-directive way in order to facilitate autonomous reproductive decision-making. This applies to most couples asking for assisted reproduction because of fertility problems. Some couples applying for assisted reproduction may be at higher risk of being a carrier couple, for instance because of ancestry: in the latter case, professionals may be entitled to encourage these couples to participate in preconception ECS. Imposing ECS as a precondition for access to assisted reproduction (a so-called 'coercive' offer), however, would be disproportionate, as in absolute numbers, the risk of being a carrier couple of not yet identified recessive disorders would still be very low. An illustrative example is the incidence of Tay–Sachs disease in the Ashkenazi Jewish population. Compared with the general population, Ashkenazi Jews are 10 times more likely to be carriers of this fatal disorder. In absolute numbers, however, they have a carrier risk of 1 in 31, leading to a risk of 1 in 961 of being a carrier couple, and a risk of only 1 in 3844 of giving birth to an affected child (Gross *et al.*, 2008).

Step 2: Professionals may well justifiably recommend proven carrier couples to consider preventative options, and even make access to assisted reproduction conditional on the patients' use of such options—even though a 'coercive offer' entails a very directive approach. If we follow the reasonable welfare standard, such conditional access may be justified both in exceptional cases of disorders that would make life intolerable for the child (e.g. Tay–Sachs disease, Canavan disease, Herlitz junctional epidermolysis bullosa), and with regard to conditions that may not involve unbearable suffering, but nonetheless greatly restrict the range of life plans that humans typically value and choose, and in general have a huge impact on the quality of life of affected persons (e.g. CF and Usher syndrome).

Though PGT-M may well be the most evident preventative option for many carrier couples, in practice people may prefer the use of donor gametes or prenatal diagnosis instead, for example because PGT-M is not reimbursed in their country and they cannot afford to pay themselves. To insist, then, that carrier couples should make use of PGT-M as a precondition for access to assisted reproduction would be unjustifiably restrictive. Doctors involved in assisted reproduction may feel unease when a carrier couple declines PGT-M and asks for access to assisted reproduction with the intention to have prenatal testing and termination of pregnancy in case of a 'positive' test result. After all, this may generate a dilemma: should this wish be respected, trusting that the couple will indeed try to avoid the birth of a seriously handicapped child? Or should one abstain from giving access to assisted reproduction, because couples may change their minds or even betray the professional? Although there may be no single solution for this dilemma, assisted reproduction in such carrier couples may well be justified after extensive counselling. This opinion mirrors a former ESHRE Opinion about a possible transfer after 'failed PGT', entailing a similar dilemma (De Wert *et al.*, 2014).

The above shows that, when there is a high genetic risk of serious suffering, concerns related to the welfare of the future child may limit

the reproductive options available to carrier couples applying for assisted reproduction. This also means that the aim of preconception ECS to patients seeking assisted reproduction is somewhat mixed. When the predicted level of well-being of the future child can be expected to fall below the reasonable welfare standard, the professional involved should make access to assisted reproduction conditional on the patients' use of preventative measures, as the alternative would be to disregard professional and parental responsibilities. We suggest that the preventative options created by new genomic testing possibilities are not morally indifferent and may have implications for the operationalization of both parental and professional responsibilities. Instead of ignoring these responsibilities, the screening and counselling process should enable and motivate the involved parties to live up to them (van der Hout et al., 2019).

## Couples or individuals?

In the context of carrier screening for *autosomal* recessive disorders, there is much discussion about how to report the test results to patients: is it preferable to give them to the individual partners or to approach couples as a 'reproductive unity'? In the latter case, the result 'screen-positive' would imply that both individuals are identified as carriers and 'screen-negative' that at least one individual is not identified as a carrier. Clarke is critical about couple testing as this would entail that 'couples in which only one individual is identified as a carrier are not given that information' (Harper and Clarke, 1997). These couples have nonetheless a greater residual risk of having an affected child than couples in which none of the partners have tested positive. Clarke furthermore states that 'in general, tests should not be performed if the results will be withheld from the individuals concerned' (Harper and Clarke, 1997). Withholding this information would not only restrict the reproductive autonomy of the individuals concerned but would also deny members of a carrier's extended family the opportunity to seek genetic counselling. However, if we consider that the autonomy paradigm does not seek to enable reproductive choice *per se*, but is aimed at enabling *meaningful* reproductive choices, reporting individual test results might not be that obvious. Based on this qualification, couple-based results of carrier screening for autosomal recessive conditions are particularly relevant, as only *carrier couples* have a greatly increased risk of 25% in each pregnancy that their child will be affected. Furthermore, the additional costs of an individualized approach are considerable, especially when taking account of the need for post-test counselling (see section 'Justice').

## Proportionality

What about the proportionality of offering preconception ECS to patients seeking assisted reproduction: do the possible benefits clearly outweigh the possible harms?

### Possible benefits

In the literature, it has been argued that universal ECS may be beneficial for a variety of reasons. Many of these also apply to an offer of preconception ECS to patients seeking assisted reproduction. Firstly, if patients are informed about their positive carrier status, they can avoid suffering of their future children and their own families by taking preventative measures. Moreover, if conducted in the preconception period—which is necessarily the case in the context of assisted

reproduction—ECS may optimally provide patients with a diversity of reproductive options and time for reflection. Clearly, this benefit presumes the provision of adequate information and counselling (see below). Thirdly, informing blood relatives of carriers of their *a priori* higher carrier risk may avoid suffering and facilitate informed reproductive choice. Finally, it has been argued that carrier screening may enable close prenatal and neonatal monitoring of possibly affected children, thereby contributing to early detection and a better prognosis (Henneman et al., 2016).

### Possible harms and disadvantages

Commentators mention a set of highly different possible disadvantages and risks of ECS. Some of these are societal or socio-cultural, in that they regard possible risks for 'wider society' ('socio-cultural harms'), while another cluster of risks considers harms for the members of the target group of ECS or, more specifically, the people participating in the screening. No doubt, there is some overlap between these subsets of risks.

**Socio-cultural harms and disadvantages.** Critics regularly seem to claim that the first subset of risks of preconception ECS are prohibitive. Possible societal risks include:

The 'disability rights critique'. In fact, this is a cluster of arguments including both the 'expressivist' argument, stating that the offer of such screening entails a discriminatory message towards people affected with the relevant disorders, and the 'loss of support' argument. The latter argument suggests that if in the future the numbers of affected people drop, the provision of adequate medical care and societal support for affected people may be undermined. The 'expressivist argument', however, arguably assumes that the dignity of people affected with the diseases screened for would be undermined by reproductive screening. This assumption is logically and empirically debatable, if not unsound. The rights and citizenship of affected people are unlikely to be denied. The 'loss of support' argument is, likewise, difficult to accept. First, the opposite claim can be made that more resources will be available for fewer patients, which will result in better care. Second, we would not claim that it is desirable to have more people with currently rare diseases, merely to heighten the degree of support. Third, this argument is inconsistent with other practices, such as the recommendation that prospective mothers take folic acid to prevent neural tube defects (Buchanan et al., 2001). Thus, while the concern of loss of support is a societal point of attention as we move forward, it is not a counterargument against ECS.

The 'medicalization critique'. Some critics consider carrier screening to be just another example of problematic medicalization of reproduction. Medicalization, however, is a 'moral species' term; it is important to unravel the argument to clarify what this objection really entails. It is difficult to reject the medicalization of reproduction if and insofar as this would prevent serious suffering and handicaps in future children and families. The medicalization critique is often inspired by the so-called 'social model of disability', which points to the societal origins of suffering linked with medical impairments—think of widespread stigmatization, discrimination and exclusion. But while environments should be adapted wherever possible, and 'inclusion' is a laudable aim, many genetic diseases and handicaps are linked with disadvantages and suffering which cannot be entirely eliminated, even in an ideal society (Shakespeare, 2013). Furthermore, the force of this objection seems to be especially weak when preconception ECS is offered to patients

seeking assisted reproduction, who are already seeking reproductive help from medical doctors.

**The objection in terms of eugenics.** Like medicalization, eugenics is a 'moral species term' which may have many different meanings (Paul, 1994). It is difficult to condemn the avoidance of conceiving children affected with serious disorders insofar as this would prevent serious suffering. Problematic eugenic practices typically regard involuntary measures (think of forced sterilization). Clearly, the dominant framework for both prenatal screening and universal ECS—stressing the importance of reproductive choice—seems to be less vulnerable to the objection in terms of 'eugenics', at least as long as the screening offer concerns the identification of risks for highly penetrant diseases that severely affect the offspring. The same applies for the somewhat more ambiguous framework of preconception ECS in assisted reproduction: it would be simplistic and rhetoric to disqualify a professionals' decision to only conditionally assist in the reproduction of carrier couples at (very) high risk of having a child with a serious genetic disease as 'eugenic'. Respect for reproductive autonomy should be qualified as it does not oblige doctors involved in reproductive medicine to disregard their professional responsibilities to take account of the welfare of future children.

To conclude, the possible societal risks of carrier screening do not seem to constitute an overriding objection to preconception ECS in assisted reproduction (nor to universal ECS). This should not be a surprise, as it would be inconsistent to accept prenatal screening for congenital disorders like Down syndrome and neural tube defects if this meets internationally endorsed screening criteria and at the same time categorically condemn ECS based on these general (non-specific) societal risks.

**Individual harms and disadvantages.** The second class of risks regards individual harms and disadvantages. These include the following.

**Reproductive dilemmas.** Firstly, ECS may confront prospective parents, and especially carrier couples, with difficult reproductive decisions and even dilemmas. However, this may be seen as the price to be paid for facilitating 'informed reproductive choice'. Probably, many prospective parents will agree that it is better to be informed of a repro-genetic risk you wish to avoid, than being spared of this information and assuming the risk you want to avoid unknowingly. But clearly, the present concern underlines the general prerequisite regarding the provision of adequate pre- and post-test counselling in the context of any reproductive screening. In the context of assisted reproduction, some PGT-M patients may be faced with especially complex dilemmas: if preconception ECS reveals additional genetic risks—apart from the genetic risk that triggered them to apply for PGT-M in the first place—their dream of having unaffected children may be seriously threatened or even fall apart.

The current risk may be differentiated by taking into account the screening test *per se*. General criteria to evaluate screening tests have been provided in, amongst others, the so-called Analytic validity, Clinical validity, Clinical utility and Ethical, legal and social issues (ACCE) framework. The ACCE process includes collecting, evaluating, interpreting and reporting data on particular genetic tests, allowing policy makers to have access to up-to-date and reliable information for decision-making (<https://www.cdc.gov/genomics/gtesting/acce/index.htm>). The tests used should have high analytical and clinical validity and good clinical utility. Analytical validity is defined as the test's ability

to accurately and reliably measure the relevant genotype. Clinical validity is defined as the test's ability to detect or predict the associated handicap or disease. Clinical utility refers to the value of the information generated by the test for medical practice. For ECS, clinical utility has been specified by the European Society of Human Genetics as 'the increase in a couple's reproductive autonomy and choice' (Henneman *et al.*, 2016). Obviously, screening test characteristics are highly relevant for the evaluation of any screening programme, also because of their implications for the possible proportionality of screening; if the test used has a low analytical and clinical validity and/or a low clinical utility, this will seriously undermine the proportionality of the screening. A detailed operationalization of these criteria for preconception ECS in assisted reproduction is beyond the scope of this document. A few remarks about the test's clinical validity and utility and its relevance for the evaluation of such screening's proportionality should suffice for the moment.

Many genetic disorders show the so-called 'allelic heterogeneity', meaning that various or even many sequence variants in the relevant gene may be linked with the disease at hand. The best example may be the CF transmembrane conductance regulator (CFTR) gene, linked with CF, which shows more than 2000 variants (Sosnay *et al.*, 2013; Pereira *et al.*, 2019). Exact data about so-called 'genotype-phenotype correlations' are usually not available, and these correlations (may) differ in different ethnic populations. Obviously, this may create uncertainty, and, thus, psychological, and decision-making problems in screened individuals/couples, in different ways. Firstly, it is not always clear as to whether a given variant is linked with either a serious or a milder phenotype—some variants may even generate both mild and serious phenotypes. Secondly, the test may generate variants of unknown clinical significance (VOUS). In view of these variables, a choice has to be made between different scenarios:

- ECS should be targeted to serious and well-understood variants.
- ECS may, in addition, include variants with a variable (serious or mild) expression.
- ECS may even include variants (always) correlated with a mild phenotype.
- ECS may include VOUS as well.

If one opts for the first, most targeted strategy, the numbers of false negatives, resulting in false reassurance, will increase. Especially milder disease-causing and rare variants may, then, not be detected. If one opts for the last, most inclusive strategy, the number of VOUS will increase (Abuli *et al.*, 2016). Considering the responsibility of fertility clinics offering preconception ECS to guarantee proportionality, the experimental character of such screening and the possible huge impact on a couple's welfare and reproductive decision-making, a cautious approach is warranted, at least for the time being. Some of the implications for the handling of milder variants and variants with a variable (mild or serious) expression will be addressed in the next section. In order to avoid psychological stress and decision-making problems linked with VOUS, clinicians offering preconception ECS to patients seeking assisted reproduction are advised only to report class 4 and 5 variants, i.e. variants that are likely or definitely pathogenic.

If ECS generates VOUS, it is widely—and rightly—accepted to preferably store these findings in databanks, in order to allow their inclusion in research aimed at clarifying genotype-phenotype correlations.

In view of such research, later re-classification of test results may be necessary, for example from (presumed) pathogenic to benign, from VOUS to non-pathogenic, or from VOUS to pathogenic. This would, then, raise issues about re-contacting the couples. The implications of such storage and re-contacting for counselling and informed consent will be touched on below (Edwards et al., 2015; Vaz-de-Macedo and Harper, 2017).

While there is concern that proven carrier status may have adverse psychological consequences, like increased distress, various studies suggest that this is not a serious risk (Lakeman et al., 2009; Holtkamp et al., 2016). However, very little is known about the psychological impact of ECS, especially if this would identify people/couples as carriers of more than one recessive disorder.

**Impact of health risks for carriers.** Depending on the disorders included in the screening panel, carrier status may entail risks for later-onset disease or impairment in carriers themselves. This, for instance, regards female carriers of a pre-mutation (PM) for Fragile X syndrome (FXS); these women are at increased risk for both premature ovarian insufficiency (POI) and the Fragile X-associated Tremor/Ataxia Syndrome (FXTAS, a neurodegenerative disorder) (European Society for Human Reproduction and Embryology Guideline Group on POI et al., 2016). Such risks raise questions about the proper scope of, and conditions for, a responsible offer of preconception ECS in the context of assisted reproduction (see below).

**Stigmatization and discrimination.** A third risk regards (social) stigmatization and discrimination of carriers/carrier couples. Although growing awareness of the fact that ‘we are all fellow mutants together’ (Muller, 1950) may help to reduce the risk of genetic stigmatization, there are still some concerns. Discrimination was a manifest effect of early carrier screening for sickle cell disease (SCD) in the USA. Some insurance companies refused to accept carriers of SCD, wrongly assuming that (heterozygous) carriers were (homozygous) patients suffering from SCD (United States. President’s Commission for the Study of Ethical Problems in Medicine, 1983). Private health insurance companies might consider not reimbursing the treatment of and care for handicapped children whose existence could have been prevented by parents informed about their genetic risk. Clearly, such discriminatory policy would not just undermine reproductive autonomy but would also entail a grave injustice towards these children who would, then, often be deprived of adequate treatment and care. With regard to possible social stigmatization, ethnic stereotyping has been mentioned as an adverse effect of some older carrier screening programmes in the USA, targeted at the black community (United States. President’s Commission for the Study of Ethical Problems in Medicine, 1983). Universal ECS may well be an effective way to counteract such ethnic profiling.

The mostly reassuring findings regarding possible stigmatization of carrier screening so far relate to screening of fertile prospective parents. These findings, however, may not be entirely applicable to an offer of preconception ECS in the context of assisted reproduction. A recent large-scale survey has revealed that, ‘despite the increased awareness of infertility and emergence of new technologies increasing treatment success, infertility stigma persists, particularly for women’ (Slade et al., 2007; Ergin et al., 2018; Worthington et al., 2019). Couples applying for assisted reproduction because of infertility problems may feel even more stigmatized if they turn out to be carriers of the same recessive disorder.

All in all, whereas there is no consensus regarding the proportionality of universal preconception ECS, a screening offer specifically addressing patients seeking assisted reproduction might, as some proponents suggest, more easily meet the proportionality criterion. After all, members of the target group are already seeking medical assistance in reproduction and may be very willing to at least seriously consider the uptake of such screening. Furthermore, this medical context may well facilitate the provision of adequate information and counselling (see below). But even though this may seem to be a reasonable assumption, a firm conclusion regarding the proportionality of preconception ECS in assisted reproduction is premature, as there are many open questions that require further scrutiny, reflection and research (see below).

## The scope of preconception ECS in assisted reproduction

As has been mentioned in the Background section, carrier screening was traditionally targeted to one or just a few genetic conditions. NGS technologies enable people to screen for carrier status of many conditions simultaneously—even whole exome/genome sequencing and analysis (WESA/WGSA) has become possible and increasingly affordable in recent years. New technologies, however, bring new challenges and problems.

Companies offer ‘direct to consumer’ genome-wide screening packages, also for PCS (Borry et al., 2011), which seems to be strongly technology-driven and commercially motivated. Obviously, this practice, which is not accompanied by proper counselling, does not define the standard of professionals offering ECS in healthcare. What, then, is the appropriate scope of preconception ECS in assisted reproduction?

### Focus on serious congenital and childhood diseases

As the major aim of the screening is to provide prospective parents with meaningful reproductive information, the dominant view is that the analysis should be targeted; whole exome/genome analysis would simply result in information overload, undermine reproductive confidence, and distort the balance between possible benefits and harms/disadvantages of reproductive genetic screening generally and ECS particularly (Dondorp et al., 2015). But how, then, to target the analysis? There seems to be a strong consensus that ECS should primarily focus on (both autosomal and X-linked) recessive, serious, congenital and childhood diseases (Henneman et al., 2016). This focus is in-line with traditional (ancestry-based) carrier screening and seems to be reasonable, though it needs some justification and specification—and might have a provisional character.

A focus on serious conditions probably best meets prospective parents’ reproductive concerns linked with having an affected or potentially disabled child and reproductive doctors’ responsibility to avoid a ‘high risk of serious harm/suffering’. The specification that the serious disorders screened for should be primarily congenital and childhood disorders, follows the same rationale. The criterion of seriousness is, however, notably difficult to define (Vertz and Knoppers, 2002). Even if people agree about the relevance of this criterion, they regularly disagree about how this should be made operational, and, consequently, may have diverging views about what to include in the screening package. This is not to suggest, however, that any operationalization and demarcation of ‘serious’ is purely subjective

and arbitrary. It should be possible to reach some inter-subjective agreement about (the operationalization of) relevant criteria—though there will always be a grey area, where reasonable people may disagree. Recessively inherited blindness and deafness may be good examples of this grey area. General criteria for seriousness, to be further re-fined, include a lower life expectancy, intellectual disability, impaired mobility, a substantial adverse impact on ‘normal functioning’, the need for (a series of) surgical interventions—especially if these are only partly effective—and regular hospitalization, or, more generally, an adverse impact on children’s quality of life (Lazarin *et al.*, 2014; Edwards *et al.*, 2015). Both the expertise of professionals, especially professionals engaged in traditional genetic counselling and paediatrics, and the lived experience of families with affected children may well give (experiential) input to further debates about the precise content of the screening package focused on serious (congenital and childhood) disorders. This content may need continuous updating taking into account findings of such studies and progress in medical science (Capalbo *et al.*, 2019; Kaseniit *et al.*, 2019; Weisz-Hubshman *et al.*, 2019; Fridman *et al.*, 2020). The inclusion of the patient perspective is crucial in order to avoid any medical bias and one-dimensionality.

Adding to the complexity of the current issue is allelic heterogeneity (see above). Genetic variants that are associated with a milder expression of disorders that are, generally, classified as serious, should preferably not be included in ECS that focuses on serious disorders. But would it be acceptable to include genetic variants with a variable expression, generating either a serious or a mild phenotype? One could argue that by including such variants the thin line to disproportionality would be easily transgressed, also because this more permissive screening policy would invite complex ranking of ‘affected’ embryos for transfer—unless the clinic sticks to a policy to never transfer an affected embryo, even if embryos carrying such variants do not necessarily result in children affected with a serious disorder. But one could also argue that the inclusion of such variants would not necessarily undermine the proportionality of ECS—on the contrary, it could even increase its proportionality, also by facilitating better embryo ranking. Whatever the outcome of this balancing, the clinic’s handling of genetic variants with a variable expression should be addressed in pre-test counselling (see below).

Symptomatic of the threat of a technological imperative—referring to the idea that emerging technologies are inevitable and must be embraced—is not just the risk that carrier screening will be ‘maximally expanded’ without evidence of its proportionality, but also that ECS panels ‘often include conditions for which carrier screening of the general population is not recommended by current practice guidelines’ (Edwards *et al.*, 2015). A good example is the inclusion of FXS. In the grey area of PMs, the risk of expansion to a full mutation (FM) may be difficult to predict. Furthermore, the phenotype—especially the possible intellectual disability—of future daughters with an FM is notably difficult to predict. And last but not least, as said, female PM carriers are at high risk of both POI and FXTAS, blurring PCS and pre-symptomatic diagnosis of late(r)-onset disorders (Grody, 2016; Willemsen and Kooy, 2017). This is not to say that carrier screening for FXS is necessarily unsound, but it illustrates the complexities involved.

The challenge, then, is to make sure that specific disorders are only included in any ECS panel—either offered to the general population or particularly addressing patients seeking assisted reproduction—if this seems to be proportionate, given the available evidence.

### *Smaller-scope ECS?*

Various arguments may be proposed to limit the scope of ECS, including:

Firstly, one might argue that disorders which are included in newborn screening (NBS) need not be included in/should be excluded from the screening panel. Think of, for example, SCD and CF. This criterion is, however, debatable and would limit the scope of ECS for no good reason, in view of the different aims of these screening programmes. While NBS primarily aims at early detection and timely treatment of affected new-borns, in order to improve their prognosis, ECS serves informed reproductive decision making of prospective parents. For those NBS conditions (inborn errors of metabolism) where affected infants may die before the NBS result is communicated, or where part of the health damage involved cannot be avoided after NBS, it could be proportionate to also add the condition to the ECS panel (Kirk *et al.*, 2020). These programmes should, then, be conceived of as complementary (Wilfond, 2009). The existence of NBS does not render ECS unsound or unnecessary.

Secondly, the scope of ECS should, some argue, be limited to the availability of and eligibility to (i.e. indications accepted for) PGT-M in the given jurisdiction. Clearly, ‘patients should not embark on ECS under the belief that the option of PGT-M will be unquestionable in light of a positive result’ (Vaz-de-Macedo and Harper, 2017). But although the composition of ECS panels should ideally be linked to the availability of PGT-M for the same disorders, we doubt as to whether the first should be necessarily limited to the latter. First, a broader composition of the ECS panel could be a catalyst for widening the eligibility to PGT-M in more restrictive jurisdictions.

Secondly, even if PGT-M is not available for a subset of serious conditions in particular jurisdictions, ECS including these conditions could still facilitate informed reproductive choice (though, more limited) by either offering other types of reproductive avoidance (for instance, donation and adoption) or by carrier couples’ willingness to seek PGT-M abroad. Clearly, this needs further debate.

### *Broader-scope ECS?*

Obviously, one may also consider broadening the ECS panel, and include, for example disorders manifesting a different inheritance pattern.

One could include, for instance, (selected) autosomal *dominant* (AD) disorders (as some programmes do), focussing mostly on *early* onset AD disorders (Abuli *et al.*, 2016), e.g. autosomal dominant polycystic kidney disease (Gimpel *et al.*, 2019) or possibly Alexander disease (Battaglia *et al.*, 2019), but maybe also *late* onset AD disorders, like Huntington’s disease (HD), ‘early-onset’ dementias, and some hereditary cancer syndromes. As for any (widening of a) screening programme, the prerequisite of proportionality is of paramount importance. Importantly, the possible benefits of such wider ECS panel may be less clear, as higher penetrance AD disease-causing variants will often be already known among the members of seriously affected families (generating an indication for pre-symptomatic diagnosis in relatives of the probands). Furthermore, such widening of the scope of ECS may have serious disadvantages and drawbacks, for various reasons. To mention just a few: this would blur ECS and pre-symptomatic testing for late-onset disorders, informing patients about genetic health risks for both their possible children’s and for their own future health, generating additional concerns and anxieties. Some

disease-causing variants for later-onset disorders are ‘actionable’ (in the traditional meaning of enabling primary/secondary prevention for the benefit of the carrier), others are not—but may still be relevant for carriers’ reproductive decision-making. Clearly, the meaning and mixing up of two types of ‘(non-) actionable’ may be confusing for many people. Furthermore, the penetrance of AD disease-causing variants in the general population may be lower than the penetrance of such variants in affected families. This may, paradoxically, increase the emotional load of testing for such variants.

Secondly, one could consider adding mitochondrial (mt) disorders that are maternally transmitted caused by disease-causing variants in mtDNA to the ECS panel. Given the existence of an early germline bottleneck, currently carrier screening for such disorders may have only very limited value (Marchington et al., 2010). Again, such widening would add practical difficulties and complex counselling issues. Think particularly of the lower predictive value of relevant mtDNA variants and the limited value and availability of reproductive options like PGT, prenatal diagnosis and—highly experimental—mitochondrial replacement therapy (Hallowell, 2012).

In view of this, broader-scope ECS (including carrier screening for late-onset diseases and for disorders caused by variants in mtDNA) is currently not considered the best option. There are simply too many uncertainties and unknowns. Restricting ECS to serious AR congenital and childhood disorders has the largest chance to be proportional for the moment.

A linked question for further debate is whether and, if so, on what conditions, it would be sound to offer ‘personalized’ preconception ECS to patients seeking assisted reproduction, allowing them to determine (or at least engage in shared decision making regarding) the scope of their ‘personal’ ECS panel. Though such personalization may, at least in theory, be in line with the principle of respect for (reproductive) autonomy, one of the questions to be addressed is how informed consent models could be developed that can be adequately made operational in clinical practice without undermining the quality and legal validity of the counselling.

## Justice

From a justice perspective, various types of considerations are important, including the examples below.

In terms of economy, are the so-called ‘opportunity costs’ of reproductive genetic screening—generally and of preconception ECS in assisted reproduction particularly—justified, especially when considering the just distribution of scarce resources for healthcare? A similar question is raised with many other provisions in healthcare, including assisted reproduction itself. Lack of funding will result in inequity. With restricted budgets, however, some ‘prioritization’ seems to be unavoidable. Still, in view of the importance of reproductive screening (at least partial) funding may be considered, in principle, insofar as such screening may help to prevent serious suffering, facilitates ‘just choices’ (Stapleton et al., 2019) and meets relevant capabilities (Nussbaum, 2011). Even though the primary aim of any reproductive genetic screening is *not* to reduce healthcare costs (see before), the fact that ECS may, in fact, save money in the long run that could be used to meet other healthcare needs, is a relevant factor to be taken into account in the calculus.

One needs to also consider justice with respect to equity. Obviously, there is not one single carrier screening practice or policy in Europe. Two types of situations may be distinguished:

- In some countries, targeted PCS is already ‘universally’ offered to the public. The best example may be Cyprus, where all prospective parents are offered carrier screening for haemoglobinopathies at the premarital stage. In those countries, the principle of equity requires that both (fertile) couples engaging in sexual reproduction and couples applying for assisted reproduction (either for reasons of subfertility or for genetic reasons) receive the offer of (targeted or expanded) carrier screening. The main question to be addressed, then, is whether the moral framework for carrier screening in these two different contexts is the same or not.
- Most countries do not (yet) offer any type of carrier screening, let alone ECS. Would a selective offer of preconception ECS to patients seeking assisted reproduction, then, be justified—taking account of the equity requirement? Would it be sound to selectively offer ECS to this subgroup, while all other prospective parents have the same a priori risk? Some may argue that this would be at odds with formal justice and the non-discrimination principle, as similar cases should be treated similarly. But one may argue that there are relevant differences that may justify differential treatments. Firstly, professionals involved in assisted reproduction carry responsibilities regarding both the optimization of treatment and the welfare of the possible future child. A second argument could be that selective ECS for patients seeking assisted reproduction more easily meets the proportionality requirement (than universal ECS), in that these patients are already in the process of assisted reproduction (often IVF, sometimes even IVF/PGT-M), and adequate counselling may be easily guaranteed. If one does not consider these arguments to be convincing, a selective offer of preconception ECS to patients seeking assisted reproduction might still be—albeit just temporarily—justified as part of a learning trajectory towards possible future, universal, implementation of ECS. Obviously, we must be cautious about ‘upselling’ lucrative genetic screening to patients who are in a somewhat vulnerable position towards their fertility doctor/clinic. Patient interest, not commercial interest, should determine clinical care. As indicated, the physician’s responsibility for the welfare of the future child should not be used as a rhetorical tool to prematurely implement experimental ECS in assisted reproduction as a self-evident, routine strategy, let alone to make ECS obligatory for all patients.

## Informed consent and the art of counselling

Informed consent and counselling are primarily instruments to make respect for autonomy operational. Though intertwined, the two are not the same; while the information to be provided regards the relevant (medical) facts and procedures, counselling aims at helping couples to make a decision, first and foremost by linking the relevant facts with their personal needs, values and preferences.

When it comes to the definition of good clinical practice generally and adequate informed consent particularly, clinicians should always take account of the relevant legal norms in their countries’ jurisdictions. From an ethical point of view, general requirements are that the

information provided is adequate and that the consent solicited is voluntary.

Two requirements are especially important when it comes to the provision of information. First, especially in the context of a screening trajectory, the provision of information and counselling is not one single event, but a process, taking account of both the whole trajectory and the specific step at hand (Health Council of the Netherlands, 2001). In the context of the preconception ECS trajectory, at least three steps/moments can be distinguished: first, the offer of and decision about participating in the screening; second, the offer of and decision about reproductive options for carrier couples identified by the screening; and, third, if a carrier couple participates in PGT-M and the embryos prove to be affected, the offer of and decision about the options then available, including: no transfer (and possibly the start of another IVF-ICSI/PGT-M cycle) and, possibly, ranking (Human Fertilisation and Embryology Authority (HFEA), 2019).

A second aspect regards the so-called standard of disclosure. The 'reasonable person' standard, which defines what reasonable persons generally need to know in order to be able to make an informed decision, should be used as the initial standard of disclosure. This standard has to be supplemented by the 'subjective' standard, which judges the adequacy of information by reference to the specific informational needs of the individual person (Beauchamp and Childress, 2013). The individual or couple seeking screening should, then, always be invited to bring their questions and concerns. Consequently, the informed consent process should, at least partly, have the character of a dialogue.

Clearly, the information to be provided, like the issues to be addressed in related counselling, is highly dependent on the content and scope of the screening offered. The wider the scope of the screening, and the more comprehensive the categories of variants one wants to communicate (including variants with a variable expression and VOUS), the more challenging it will be to obtain people's truly *informed* consent. Without suggesting an exhaustive list for the provision of adequate information and counselling at each of the moments in the process, the points to consider include the following:

Firstly, regarding ECS per se: as a starter, the professional should briefly introduce this option and ask the patients whether they want to know more about this screening. If so, the professional may then give some more information and offer counselling.

Clearly, it is not practical for a clinician to clarify and discuss each disease included in multi-disease screening panels in detail (Grody *et al.*, 2013). The implication of offering ECS must, then, be that some sort of 'generic consent' is implemented. Even though such generic consent may be morally justified (as 'good enough'), some complex questions need further reflection, most importantly: how to guarantee that generic consent is being made operational as a (reasonable) variant of informed consent—not as a (problematic) alternative for informed consent?

While it is sometimes suggested (Edwards *et al.*, 2015) that information about carrier couples' reproductive options can and should be postponed and be given in the context of *post-test* counselling, this information should—though roughly—be provided in the context of *pre-test* counselling, like global information about professional responsibility for the welfare of the future child and decision-making authority regarding the handling of possibly affected PGT-embryos. Likewise, the

possible relevance of the findings of ECS for relatives, and the clinic's policy regarding the handling of possible 'conflicts of duties' should be ticked off in pre-test counselling.

In view of both the lack of experience of patients with the genetic disorders included in the ECS panel and the complexity of this screening, it is to be expected that a sound offer of ECS will require substantial counselling facilities—with substantial logistic and financial implications (cf. the section on Justice). It should not be assumed that an adequate level of understanding 'can be achieved quite easily for couples that ask for pregestational genetic counselling and for those that are in the process of ART' (Abuli *et al.*, 2016). Importantly, the majority of patients have a fertility problem (not a genetic problem), and although the subset of couples that apply for PGT-M will expect a discussion of their genetic situation, they will probably not expect the offer of preconception ECS for totally different genetic problems. Especially members of the latter subgroup may sometimes be confronted with a combination of genetic problems, generating an indication for 'combination' PGT-M, i.e. PGT-M for both the original indication and, simultaneously, for the disorder identified through ECS (Dondorp and de Wert, 2019). This may culminate in a situation in which all embryos tested with PGT-M will prove to be affected, even more so if PGT-M is combined with aneuploidy screening (PGT-A; formerly termed preimplantation genetic screening (PGS) for aneuploidy) or if PGT-M is based on so-called haplarithmisis, which may simultaneously identify (selected) aneuploidies (Masset *et al.*, 2019). The wider the scope of PGT, the higher the risk that couples will have no child at all.

An important part of the information provided regards their *a priori* risk of having a child affected with a condition included in the ECS-panel and expectation management; patients may wrongly assume that ECS guarantees the birth of a healthy child. Clearly, 'risk-free' reproduction is an illusion, even in the era of reproductive genomic medicine. There is always a residual risk, in various ways; even ECS will focus on just some categories of disorders and on just a subset of variants (possibly) linked with the disorders included in the screening panel.

As said, though some personalization of ECS may, at least in theory, be in line with the principle of respect for (reproductive) autonomy, further debate and research is needed to determine how informed consent models aimed at personalization could be developed that can be adequately made operational in clinical practice.

Secondly, carrier couples identified need to be informed and counselled in more detail about the reproductive options available. Regarding PGT-M, especially possible tensions linked with the decision making authority about the (non-)transfer of affected embryos need closer attention. Likewise, the implications of patients' proven carrier status for relatives will be a more pertinent part of the agenda now, especially when a woman proves to carry an X-linked disease.

Thirdly, when preimplantation embryos prove to be affected with a disorder included in the ECS panel, detailed counselling is crucial. This will generally regard primarily the 'pros and cons' of a possible additional IVF-ICSI/PGT-M cycle and the possible donation of affected embryos for research purposes. In some situations, there may be additional issues to be counselled in detail, especially when preimplantation embryos are shown to have a milder anomaly, for example, a milder variant of a serious disorder screened for, or a milder chromosomal aberration detected via haplotyping or via additional PGT-A, like

47, XXY (Klinefelter's syndrome). Additional counselling may also be required when embryos have an unclear risk status, for example after PGT-failure (when PGT does not generate a diagnosis), when the embryo carries genetic variants with a variable expression, or when supplementary PGT-A shows an embryo to have an autosomal trisomy, like trisomy 21, with a *mitotic* origin. In such cases, ranking embryos for transfer may be considered, depending on the harm/probability-ratio in given cases. An in-depth reflection on (counselling issues linked with) ranking is beyond the scope of the document.

No doubt, research on informational and counselling needs and on the adequacy of information and counselling provided in the context of each of these steps in (pilots for) ECS is crucially important. The same holds true for the role and (implicit) value judgements of algorithms used for ranking.

## Conclusions and recommendations

When considering or providing preconception ECS to patients seeking assisted reproduction, clinicians should always take account of relevant medico-legal norms in their countries' jurisdictions.

Presumed 'categorical' ethical objections to preconception ECS in assisted reproduction are not convincing. Such screening may well be morally justified, if and insofar as it meets the proportionality criterion.

A firm conclusion regarding the proportionality of preconception ECS in assisted reproduction is premature, as relevant genetic, epidemiological, economic and especially psychological data are lacking. There are many open questions that require further scrutiny, reflection and research, including for instance the interest in screening of couples seeking assisted reproduction, their reproductive choices after 'positive' results, the impact of screening on their welfare, the impact of possible tensions between a doctor's professional responsibility and the reproductive autonomy of patients, the scope of the screening panel, etc.

It is crucial that preconception ECS in assisted reproduction is embedded in rigorous research protocols with appropriate reporting. Furthermore, education of the public, as well as of medical students and professionals will be needed after research outcomes have become available. The 'evidentiary' model (Wilfond and Nolan, 1993) requires adequate pilot studies and continuous monitoring and evaluation (Edwards et al., 2015).

According to the dominant view, the primary aim of universal carrier screening—i.e. a targeted or ECS offer to the general population—should be to facilitate reproductive choice. The aim of preconception ECS in assisted reproduction, however, is mixed in view of the dual responsibility of doctors involved in assisted reproduction. While the screening offer itself should be non-directive, it is good clinical practice to give carrier couples of serious disorders—i.e. those that do not meet the 'reasonable welfare' standard as accepted by ESHRE—access to assisted reproduction only on condition that they opt for 'avoidance' and apply for PGT-M, donor gametes, or, maybe, prenatal diagnosis.

Preconception ECS in assisted reproduction should preferably be limited to recessive, serious, congenital and childhood disorders and to class 4 and 5 variants linked with these disorders, at least to start

with. A possible broadening of the scope of preconception ECS in assisted reproduction requires adequate research and interdisciplinary debate.

The proper operationalization and feasibility of generic consent in preconception ECS in assisted reproduction needs further debate.

Counselling should always be offered. It should not take a back seat, as adequate counselling is a necessary condition for guaranteeing the proportionality of preconception ECS in assisted reproduction. To enable couples applying for assisted reproduction to make a well-informed decision about participating in ECS, information about carrier couples' reproductive options, taking account of professional responsibilities, should already be provided in the context of pre-test counselling.

A facilitating and co-ordinating role of ESHRE regarding research and reflection aimed at the development of evidence-based, responsible guidelines on preconception ECS in assisted reproduction is highly recommended. This should include minimum requirements regarding clinical and analytical validity and the refinement of criteria to determine the scope of ECS.

The current recommendations should be evaluated periodically, also taking account of new reproductive options that may become available in the years to come, notably non-invasive prenatal diagnosis (NIPD) very early in pregnancy and germline genome editing.

## Disclaimer

This Ethical document represents the views of ESHRE, which are the result of consensus between the relevant ESHRE stakeholders and, where relevant, based on the scientific evidence available at the time of preparation.

The recommendations should be used for informational and educational purposes. They should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. They do not replace the need for application of clinical judgement to each individual presentation, nor variations based on locality and facility type.

Furthermore, ESHRE's recommendations do not constitute or imply the endorsement, recommendation, or favouring of any of the included technologies by ESHRE.

## Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

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## Authors' roles

G.D.W. and S.V.D.H. drafted the argumentation of the paper. N.V. provided methodological and logistic support. All other authors contributed equally to discussing the text and all approved the final version. The members of the ESHRE Ethics Committee (see appendix) provided comments and approved the final version.

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## Conflict of interest

M.G. works at the Department of Reproductive Medicine of the Amsterdam UMC (location AMC and location VUMC). Location VUMC has received several research and educational grants from Guerbet, Merck and Ferring.

## Appendix

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